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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/920,286	08/02/2001	Xiaobin Zhao	0623.1110001/JMC/MGP	3882

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EXAMINER	
LEWIS, PATRICK T	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 08/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/920,286	ZHAO, XIAOBIN	
	Examiner	Art Unit	
	Patrick T. Lewis	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,11-21 and 24-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,9,12-21 and 24-35* is/are rejected.

7)☒ Claim(s) *5-8 and 11* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *03152004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's Response dated April 16, 2004

1. In the Response filed April 16, 2004, claims 24-35 were added. Claims 1-9, 11-21, and 24-35 are pending. An action on the merits of claims 1-9, 11-21, and 24-35 is contained herein below.

2. The objection to claims 13-14 and 20 has been withdrawn.

3. Applicant's arguments with respect to claims 1-9, 11-12, 15-19, and 21 under 35 U.S.C. 112, first paragraph, have been fully considered and are persuasive. The rejection of claims 1-9, 11-12, 15-19, and 21 has been withdrawn.

Specification

4. The disclosure is objected to because of the following informalities: the disclosure does not contain Brief Description of the Drawings.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 27-28 and 33-34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s)

contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The disclosure, as originally filed, does not support applicant's claims to compositions wherein a therapeutically active agent is bound to the instantly claims cross-linked HA through physical means. The disclosure does not support applicant's claims to compositions wherein a therapeutically active agent is bound to the instantly claims cross-linked HA through chemical means. Applicant alleges support for the newly added claims on pages 15-16 of the disclosure. The disclosure states that therapeutically active factors may be bound to the crosslinked HA derivative by methods well known in the art; however, no support is found for the narrower claim language limiting the binding of the crosslinked HA and therapeutic agent through physical or chemical means. The introduction of claim changes which involve narrowing the claims by introducing elements or limitations which are not supported by the as-filed disclosure is a violation of the written description requirement of 35 U.S.C. 112, first paragraph.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1-4, 12-13, 15-18, 20-21 are rejected under 35 U.S.C. 102(b) as being anticipated by Tomihata et al. *Journal of Biomedical Materials Research* (1997), Vol. 37, pages 243-251 (Tomihata).

Tomihata discloses a crosslinked HA film containing amide and ester bonds (pages 247-248). L-Lysine methyl ester (crosslinking agent 1) was added to an 80 vol % ethanol / 20 vol % water mixture and the crosslinking of HA was allowed to proceed in the medium in the presence of 10 mM water-soluble carbodiimide (crosslinking agent 2).

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

11. Claims 1-4, 9, 12-21, and 24-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tomihata et al. *Journal of Biomedical Materials Research* (1997), Vol. 37, pages 243-251 (Tomihata) and Nguyen US 5,690,961 (Nguyen) in combination.

Claims 1-4, 9, and 12-14 are drawn to a process for the preparation of multiple cross-linked derivatives of hyaluronic acid (HA), which process comprises covalently cross-linking HA via two or more different functional groups, wherein said cross-linking is effected by contacting HA with one or more chemical cross-linking agents so as to form two or more chemically distinct cross-links, between said HA molecules. Claim 2 limits the functional groups cross-linked. Claim 3 limits the types of bonds formed. Claim 4 limits the cross-linking agent. Claims 9, 12 and 14 limit the order in which each type of functional group is cross-linked. Claim 13 limits the cross-linked HA produced. Claims 15-20 are drawn to a multiple cross-linked HA. Claims 16-17 limit the bond types. Claims 18-19 limit the form of the cross-linked HA. Claim 21 is drawn to a product comprising a multiple cross-linked HA. Claims 24-35 are drawn to a composition comprising a multiple cross-linked HA and one or more therapeutically active agents. Claims 25-26 and 31-32 limit the therapeutically active agent. Claims 27-28 and 33-34 limit how the crosslinked HA and therapeutic agents are bound. Claims 29 and 35 limit the form of the composition.

Tomihata teaches a crosslinked HA film containing amide and ester bonds (pages 247-248). L-Lysine methyl ester (crosslinking agent 1) was added to an

80 vol % ethanol / 20 vol % water mixture and the crosslinking of HA was allowed to proceed in the medium in the presence of 10 mM water-soluble carbodiimide (crosslinking agent 2). The inclusion of amide bonds enhances the hydrolytic stability of the cross-linked HA (page 350). Tomihata further teaches that HA is used in orthopedics for the treatment of joint disease, in cosmetics, and in drug delivery systems (page 243).

Tomihata differs from the instantly claimed invention in that 1) Tomihata does not teach crosslinking each type of functional group sequentially; 2) Tomihata does not teach the multiple cross-linked HA in the form of a gel; and 3) Tomihata does not teach a composition further comprising one or more therapeutically active agents.

Nguyen teaches HA crosslinked with dianhydrides via ester bonds (column 1, lines 6-13; column 3, lines 13-50; column 11, lines 1-19). The crosslinked HA may be used as a drug delivery vehicle. The crosslinked HA forms a molecular cage in which molecules with pharmacological activity can be dispersed. The substances contained in the cage are delivered into the environment by diffusion. The drug molecule, or mixture or drug molecules, may be covalently or non-covalently bonded to the HA. The gels, films, threads particles or sponges of the crosslinked HA may be placed, sprayed, ingested, injected or implanted at the location where the contained pharmacological substance is needed. These substances may be therapeutic drugs (such as anesthetics, analgesics, anti-inflammatories, antibiotics, hormones, or cytostatics), growth factors, enzymes or cellular anti-adhesion compounds.

It would have been obvious to one of ordinary skill in the art at the time of the invention to crosslink each type of functional group sequentially. The selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected results. It would have also been obvious to one of ordinary skill in the art at the time of the invention to use the multiple crosslinked HA of Tomihata as a drug delivery vehicle for active agents such as anesthetics, antibiotics, or growth factors since crosslinked HA is well known in the art as a drug delivery vehicle. The selection of a known material based on its suitability for its intended use is prima facie obvious. The formulation of a therapeutic composition into a gel is seen to be well within the purview of one of ordinary skill in the art. Crosslinked HA in gel form is well known in the art. Reciting an old composition (i.e. multiple crosslinked HA of Tomihata) in a new physical form (i.e. gel) only incidentally related to its unobvious utility will not impart patentability thereto. One of ordinary skill in the art would have been motivated to select a particular formulation based on the site of administration and treatment regimen.

Conclusion

12. Claims 1-9, 11-21, and 24-35 are pending. Claims 1-4, 9, 12-21, and 24-35 are rejected. Claims 5-8 and 11 objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. No claims are allowed.

Contacts

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patrick T. Lewis whose telephone number is 571-272-0655. The examiner can normally be reached on M-F 10:00 am to 3:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patrick T. Lewis, PhD
Examiner
Art Unit 1623

ptl
August 4, 2004